A Synopsis

On

STUDIES RELATED TO SOME MICHAEL ACCEPTORS

For

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CONTENTS

SR. NO.	TITLE
1	INTRODUCTION
2	REVIEW OF LITERATURE
3	METHODOLOGY
4	SIGNIFICANCE OF RESEARCH WORK
5	REFERENCES

1. INTRODUCTION

The activated α, β- unsaturated compounds are called Michael acceptors which are used as building blocks for synthesis of several biodynamic and heterocyclic systems and have received a wide attention due to their significant vast pharmacological activities. In recent years Michael acceptors have emerged as a versatile synthetic intermediate on account of their readily accessibility and high reactivity. Although the Michael reaction has been around over the decades, it has become a part of the main stream of the organic Chemistry.

The Michael reaction or the Michael addition of a carbanion or another nucleophiles to an alpha beta unsaturated carbonyl system. Michael addition of carbon nucleophiles to electron deficient olefins as a classical and fundamental carbon-carbon bond forming reaction. This reaction and its close variants have been extensively used for the synthesis of highly functionalized heterocycles. Due to their biological activity and synthetic utility as intermediates in the synthesis of several biodynamic heterocycles, these systems are one of the most versatile synthons for various chemical transformations. Chalcones (1, 3-diarylpropenones) having α, β-unsaturated carbonyl system are important Michael acceptors and constitute an important class of biologically active flavonoids and are considered as useful intermediates. The Chemistry of chalcones as Michael acceptors is considered to be one of the most dynamic and challenging area of Chemistry embracing a vast spectrum of advances of both theoretical and practical relevance.

Keeping in view the potential pharmacological uses of Michael acceptor derivatives the objectives to be achieved in the research are as under:

- To synthesize differently substituted Michael acceptors by conventional and microwave assisted methods.

- To transform these compounds into different sized bioactive compounds using suitable bidentate reagents.
- To systematically identify and characterize the synthesized compounds by elemental and spectral analysis.
- Biological evaluation of the synthesized compounds and correlate their structure activity relationship.

2. REVIEW OF LITERATURE

Michael acceptors include several early studies which had become classics in the literature of synthetic organic chemistry[1]. There are basically four types of Michael acceptors:

- 1, 3-diarylpropenone known as chalcone
- Phenyl vinyl ketone
- 1, 4-diphenyl-2-butene-1, 4-dione (dibenzoylethylene)
- Methyl vinyl ketone

Chalcones as Michael Acceptors

Chalcones are the compound where aromatic substitutents are introduced into the terminal position of the system C=C-C=O. These compounds are also known as benzylidene-acetophenones, benzalacetophenones, phenylstyryl ketone or 1, 3-diaryl-propenones. Introduction of aromatic substitutents increases the polar character of this enone system and therefore its tendency to undergo the Michael condensation. A very large number of such reactions have been carried out using dichlorochalcones[2], α-cyanochalcones[3] and α-phenylchalcones[4-5]. The synthetic utility of Michael acceptors and their heterocyclic

analogues is also demonstrated as they undergo reaction with different reactants e.g. ketones[6-10], acetophenones, benzophenone, phenyl benzylketones, cyclopentanone, 3-methylcyclohexanone, menthone and champhor, Amine e.g. o-aminobenzenethiol[11], morpholine[12], malononitrile[13].

Synthetic Applications

A large number of synthetic possibilities of Michael type of reactions have been explored from time to time. Depending upon the nature of acceptor and conditions of the reactions, the 1, 4- or 1, 2- addition product may undergo spontaneous cyclization or cyclo-isomerization reactions leading to a large number of cyclic and heterocyclic derivatives of paramount synthetic utility[14-16].

Azepine is formed through the conjugate addition of formamides to nitroalkenes and the subsequent intra-molecular nitrile oxides cycloaddition (INOC) reaction[17]. These derivatives have been reported to be associated with diverse pharmacological activities such as anti-platelet activity[18], anti-malarial activity[19], anti-cancer activity, anti-hyperglycemic activity[20], vasopressin (AVP) antagonist activity[21]. Thiazine has been synthesized from the reaction of chalcone with thiouria in presence of KOH[22]. They are known to possess anti-malarial activity[23] and antifungal activity[24].

Aza-Michael addition of sulphonamides to α, β-unsaturated esters provides a route to protected β-amino acid synthesis[25, 26]. Different reagents have been used for aza-conjugate addition of amine to α, β-unsaturated compounds[27-29]. Looking into the multifold properties exhibited antimicrobial activity towards Mycobacterium tuberculosis[30, 31]. Michael addition of amines to α, β-unsaturated carbonyl systems gives β-amino ketones, which are attractive for their use as synthetic intermediates of anticancer agents and antibiotics[32-34]. The addition of thiol to these results in the synthesis of biologically active

compound such as calcium antagonist diltiazem[35-37]. Chalcones were subjected to Michael addition with styryl acetoacetate in presence of acetone to get cyclohexanones, which then condensate with hydrazine hydrate to afford indazole derivatives These derivatives possess variety of pharmacological activities such as analgesic, antidepressant, and antitumor activities[38]. The reaction of nucleophile like o-phenylenediamine with Michael acceptors can afford six & seven membered rings. They are associated with anti-lung cancer, anti-inflammatory agents[39]. Similarly benzothiazepines which are formed through reaction with 2-aminothiophenol are known to possess as anti-HIV, anti-coagent, anti allergenic activity. Various other bioactive rings are synthesized by using conventional[40-42] & microwave assistedl[43-48] synthetic routes.

3. METHODOLOGY

Some novel Michael acceptors have been synthesized by two routes:

(1) Conventional route

(2) Non-conventional route

The non-conventional routes basically include microwave irradiation, ultrasonic and photochemical process. The use of such non conventional reaction condition has several advantages like shorter reaction time, increase yield, selectivity in reaction, easy of reaction work-up, eco-friendliness as compared to conventional route. Thus microwave assisted synthesis becomes a part of green Chemistry.

Scheme of reaction:

- Synthesis of various substituted chalcones by using conventional and microwave assisted methods in the presence of different inorganic solid support like montmorrilonite KSF, montmorrilonite K-10, alumina-acidic, basic and neutral etc.

- Conversion of the synthesized chalcones into potentially bio-active heterocycles by the reaction with DMSO-I_2, 2-aminothiophenol, ortho-phenylenediamine, urea, thiourea, guanidine hydrochloride, cyclization using different inorganic solid support, malononitrile-mopholine etc. to form aurones, 1, 5-benzothiazepines, 3,4-dihydroquinoxaline oxazines, thiazines, pyridimine, 1, 3-dicarbonitrile derivatives etc.
- Synthesized compound will be characterized by elemental and spectral analysis.
- Evaluation of the synthesized compounds and correlate their structure activity relationship.

4. SIGNIFICANCE OF RESEARCH WORK

1, 3-Diarylpropeneone having an enone system is important Michael acceptor and involved in the synthesis of a large number of heterocyclic compounds which show profound influence on the cardiovascular, cerebro vascular & neuromuscular systems. Michael acceptors and their heterocyclic analogues have industrial application as polymers, stabilizers, sweeteners, photosensitive materials, scintillators analytical regents etc. The combination of solvent free procedures and microwave irradiation will be used to carry out a wide range of reactions within shorter reaction times and with high conversions and selectivity, yields and purity of the products as compare to those of conventional heating will generally be improved.

5. REFERENCES

1. D. N. Dhar. (1981). The chemistry of chalcones and related compounds, *Wiley-Inter Science,* New York.
2. Azarifar, D., Ghasemnejad, H. (2003). Microwave-Assisted Synthesis of Some 3, 5-Arylated 2 Pyrazolines. *Molecules,* 8, 642-648.

3. Kolosov, M. A., Orlov, V. D., Kolos, N. N., Shishkin, O. V., Zubatyukb, R. I. (2007). Reaction of α cyanochalcones with phenylhydrazine. *Arkivoc*, xvi, 187-194.

4. Asiri, A. M., Khan, S. A. (2011). Synthesis and Anti-Bacterial Activities of a Bis-Chalcone Derived from Thiophene and its Bis-Cyclized Products. *Molecules*, 16, 523-531.

5. Pratt, R. E., Welstead, Jr. W. J., Lutz. R. E. (1970). Quinoline syntheses by reaction of hydrazoic acid with α, β-unsaturated cis-chalcones. *J. Hetero. Chem*, 7(5), 1051-1055.

6. Hsieh, H. K., Tsao, L. T., Wang, J. P. (2000). Synthesis and anti- inflammatory effect of chalcones. *J. Pharm. Pharma..*, 52, 163-171.

7. Viana, G. S., Banderia, M. A., Mantos, F. J. (2003). Analgisic and anti-inflammatory effects of chalcones isolated from Myracrodruon urundeuva allemao. *Phytomed.*, 10(2-3), 189-195.

8. Fabiane, L. G, Michael, T. R., Andra., Santos, A . R. S. (2003). Trypanocidal and Leshmanicidal properties of substitution-containing chalcones. *Am. Soc. Microb.*, 1449-1451.

9. Fabio, S. S., Costantino, B. L., Vampa, G. (1998)). Synthesis and activity of a new series of chalcone as aldose reductase inhibitor. *Eur. J. Med. Chem.*, 33, 859-866.

10. Valla, A., Valla, B., Cartier, D. (2006). New synthesis and potential antimalarial activities of new' 'retinoid- like chalcones''. *Eur. J. Med. Chem.,* 41, 142-146.

11. Ghotekar, D. S., Joshi, R. S., Mandhane, P. G., Bhagat, S. S., Gill, C. H. (2010). Synthesis of some biologically important fluorinated 3-chlorocromones and 1, 5-benzothiazepines as anti-microbial & antifungal agents. *Indian J. Chem.*, 49B, 1267-1270.

12. Sharma, P., Hussain, K. F., Sukhwal, S., Kothari, S., Singhal, M., Verma, B. L. (1999). A Convenient one-pot synthesis of 2-substituted -4, 6-diaryl pyrimidines. *Indian J. Chem.,* 38B, 966-968.

13. Kidwai, M., Saxena, S., Rastogi, S. (2004). A facile one pot synthesis of 2-amino benzene-1, 3-dicarbonitrile. *Indian J. Chem.,* 2004, 2423-2425

14. Yadav, J. S., Reddy, R. A., Rao, G. Y., Narsaiah, A. V., Reddy, B. V. S. (2007). Lanthanum trichloride ($LaCl_3$): An efficient catalyst for conjugate addition of amines to electron-deficient olefins. *Lett. Org. Chem.*, 4, 462–464.

15. Azizi, N., Saidi, M. R. (2004). $LiClO_4$ accelerated Michael addition of amines to α, β-unsaturated olefins under solvent-free conditions. *Tetrahedron,* 60,383–387.

16. Li, J. T., Yang, W. Z., Wang, S. X., Li, S. H., Li, T. S. (2002). Improved synthesis of chalcones under ultrasound irradiation. *Ultra. Sonochem.*, 9, 237-239.

17. Kamimura, A., Yoshida, T., Uno, H. (2008). Stereoselective synthesis of azepines through the conjugate addition of formaamides to nitroalkene and subsequent intramolecular nitric oxide cycloaddition reaction. *Tetrahedron,* 64 (49), 11081-11085.

18. Liu, M., Wilairat, P., Go, L. M. (2001). Antimalarial alkoxylated and hydroxylated chalones: structure-activity relationship analysis. *J. Med. Chem.*, 44, 4443-4452.

19. Miranda, C. L., Stevens, J. F., Ivanov, V., McCall, M., Frie, B., Deinzer, M. L., Buhler, D. R. (2000). Antioxidant and prooxidant actions of prenylated and nonprenylated chalcones and flavones in vitro. *J Agric. Food. Chem.*, 48, 3876-3884.

20. Satyanarayana, M., Tiwari, P., Tripathi, K., Srivastava, A. K., Pratap, R. (2004). Synthesis and antihyperglycemic activity of chalcones based aryloxypropanolaamines. *Bioorg. Med. Chem.*, 12(5), 883-889.

21. Ko, H. H, Tsao, L. T, Yu, K. L, Liu, C. T, Wang, J. P., Lin, C. N. (2003). Structure-activity relationship on chalcone derivatives: the potent inhibition on chemical mediator release. *Bioorg. Med. Chem.*, 11, 105-111.

22. Kalirajan, R., Sivakumar, S. U., Jubie, S., Gowramma, B., |Suresh, B. (2009). Synthesis and biological evaluation of some heterocyclic derivatives chalcones, *Int. J. Chem. Tech. Res.,* 1, 27-34.

23. Mishra, N., Arora, P., Kumar, B. (2006) Synthesis of novel substituted 1,3-diaryl propenones derivatives and their antimalarial activity in vitro. *Eur. J. Med. Chem.,* 41, 142-146.

24. Ramdhavane, P., Karele, B. (2009). Synthesis and screening of some fluorinated dibenzofuran containing 3-chlorocromones and benzothiazines. *J. Hetro. Chem.,* 46(4), 732-736.

25. Vyas, D. H., Tala, S. D., Dhaluk, M. F., Akhbari, J. D., Joshi H. S. (2008). Synthesis antitubercular and antimicrobial activites of new pyrazoline and ixozalones derivatives. *Cheminform,* 39(33).

26. Prasad, R. Y., Kumar, P. P., Kumar, P. R., Rao, A. S. (2008). Synthesis and antimicrobial activity of some new chalcones of 2-acetyl pyridine. *E. J. Chem.*, 5(1), 144-148.

27. Evans, D. A., Fu, G. C. (1990). Conjugate reduction of α, β-unsaturated carbonyl compounds by catecholborane. *J. Org. Chem.,* 55, 5678-5680.

28. Jhala, Y. S., Dulawat, S.S., Verma, B. L. (2006). Solvent free improved synthesis of some substituted 1,3-diaryl-propenones and 3,5-diaryl-6-carboxycyclo-hexanones under microwave irradiation and their antibacterial activity, *Indian J. Chem.*, 45 B, 466-469.

29. Meei, Y. L., Yasheen, M. T., Flavin, Z. L. M., Wdiguo, N. Ching, F. (2002). Chalcones and flavonoids as anti tuberculosis agents. *Bioorg. Med. Chem.*, 10, 2795-2802.

30. Desai, J. T., Desai, K. R. (2008). Microwave enhanced heterocyclization: A convienent procedure for antimicrobial 1, 5-Benzothiazepine compounds. *Indian. J .Chem.,* 46 B, 1179-1186.

31. Patel, V. M., Desai, K. R (2005). Clean and efficient microwave solvent free syenthesis of some antimicrobial compounds from 2-aminothioiazine. *Indian J. chem* , 44B.

32. Eddarir, S., Cotelle, N., Bakkour, Y., Ronaldo, C. (2003). An efficient synthesis of chalcones based on Suzuki reaction, *Tetrahedron Lett.,* 44(28), 5359-5363.

33. Gupta, R., Gupta, N., Jain, A. (2010). Improved synthesis of chalcones and pyrazolines under ultrasonic irradiation: *Indian J. Chem.,* 49 B, 351-355.

34. Kidwai, M., Mishra, P. (2010). Ring clousure Reactions of chalcones using Microwave Technology, *Cheminform,* 30.

35. Kim, B. Y., Ahn, J. B., Lee, H. W., Kang, S. K., Lee, J. H., Shin, J. S., Ahn, S. K., Hang, C. I., Yoon, S. S. (2004). Synthesis and biological activity of novel substituted pyridines and purines containing 2, 4-thiazolidinedione. *Eur. J. Med. Chem.*, 39, 433-447.

36. Fuentes, A., Marinas, J. M., Sinisterra, J. V. (1987). Catalyzed synthesis of Chalcones under interfacial solid-liquid conditions with ultrasound. *Tetrahedron Lett.*, 28, 4541-4544.

37. Li, J. T., Yang, W. Z., Wang, S. X., Li, S. H., Li, T. S. (2002). Improved synthesis of chalcones under ultrasound irradiation. *Ultra. Sonochem.*, 9, 237-239.

38. Rao, N. S., Bajia, B., Srivastava, Y. K and Kumar, R. (2008). Microwave induced synthesis and anti-bacterial activity of some-6-(2-hydroxy phenyl)-4-(substituted phenyl)-3-oxo-2, 3, 4, 5-tetrahydro-1H- indazoles. *E-J. Chem,* 5(1), 39-42.

39. Claramunt, R. M., Sanz, D., Aggarwal, S., Kumar, A., Prakash, O., Singh, S. P., Elguero, J. (2006). The reaction of o-phenylenediamine with α, β-unsaturated carbonyl compounds. *Arkivoc*, (xiv), 35-45.

40. Prakash, O., Kumar, A., Sadana, A., Prakash, R., Singh, S. P., Claramunt, R. M., Sanzo, D., Alakarta, I., Elguero. (2005). Study of the reaction of chalcones analogs of dehydroacetic acid and O-Aminothiophenol: Synthesis and structure of 1, 5 benzo thiazepines and 1, 4-benzo-thiazines. *Tetrahedron*, 61, 6642-6651.

41. Victory, P., Bərrell, J. S., Ferran, A. D., Seoane, C., Sota, J. L. (1991). The reaction of malanonitrile with chalcones: a controversial chemical process. *Tetrahedron Lett.,* 32, 5375-5378.

42. Martin, N., Seoane, C., Soto, J. L. (1988). A convenient one step synthesis of pyrano [2, 3-] pyridines. *Tetrahedron*, 44, 5861-5868.

43. Victory, P., Larena, A. A., Germain, G., Kessels, R., Pinella, J. F., Ferran, A. V. (1995). A non-obivous reaction pathway in the formation pathway of 2-aminobenzene -1, 3-dicarbonitrile from α, β-unsaturated ketones or aldehydes. *Tetrahedron*, 51, 235-252.

44. Verma, R. S., Saini, R. K. (1997). Microwave-assisted reduction of carbonyl compounds in solid state using boron hydride supported on alumina. *Tetrahedron Lett.*, 38, 4337-4338.

45. Verma, R. S. (2001). Solvent–free accelerated organic synthesis using microwaves. *Pure Appl. Chem.*, 73, 193-198.

46. Srivastava, Y. K., Sukhwal, S., Ashawa, A., Verma, B. L. (1998). Synthesis and Reactions of Some Chalcones Containing a CF_3 Group. *J. Indian Chem. Soc.,* 29(38), 573.

47. Vibhute, Y. B., Baseer, M. A. (2003). Synthesis and activity of a new series of chalcones as antibacterial agent. *Indian J. Chem.,* 42, 202-205.

48. Saxena, H. O., Faridi, U., Kumar, J. K. (2007). Synthesis of chalcones derivatives on steroidal framework and their anticancer activities. *Steroids,* 72, 892-900.